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(54) N-alkylamides of d-(+)-carnitine having antibacterial activity, process for their preparation and pharmaceutical and cosmetic compositions containing same.

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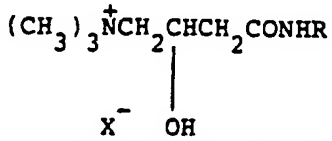
Description

The present invention relates to novel N-alkylamides of D(+)-carnitine endowed with antibacterial activity, having general formula (I)



(I)

wherein: X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}—C_{16} alkyl radical.

Preferably, X^- is Cl^-.

The present invention also relates to a process for producing N-alkylamides of formula (I) and the pharmaceutical and cosmetic compositions comprising an amount of at least one of the N-alkylamides (I) suitable for promoting an effective antibacterial action.

Some carnitine N-alkylamides are known already.

In Japanese patent 408435 filed October 31, 1960 in the name of Takeda Chemical Industries, Ltd. carnitidinamides structurally analogous to those of formula (I) are disclosed, wherein, however, the radical R is lower alkyl (methyl and ethyl). This Japanese patent discloses that such amides "promote the intestinal peristalsis and are useful as medicaments for intestinal disorders". These amides are prepared by condensing at room temperature a reactive carnitine derivative (an acid halogenide, ester or anhydride) with methylamine or ethylamine.

The N-alkylamides of D(+)-carnitine according to the present invention are on the other hand prepared via a process which comprises the following two characterizing steps:

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}—C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120—140°C, for 2—4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture a mixture of D(+)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of D(+)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110—130°C for about 34—38 hours in an atmosphere of inert gas.

After removal under vacuum of the high-boiling solvent, the residue comprising the N-alkylamide (I) is purified and the compound isolated according to known procedures.

The main advantage of the process of the present invention lies in the utilization of D(+)-carnitinamide chloride as starting material, a by-product in the L-carnitine production by resolution of racemic mixtures of D,L-carnitinamide chloride. To date, no viable utilization has been known for this by-product. Moreover, this process allows the "direct" utilization of D(+)-carnitinamide chloride to be achieved: i.e. the transamination of this process allows the direct conversion of the amide into the N-alkylamides (I) to be carried out. No intermediate steps are needed in order to convert the starting amide in one of those activated compounds (acid halogenides, esters or anhydrides) from which substituted amides are usually obtained (in this regard see the above mentioned Takeda patent). It is apparent that these intermediate steps would lower the yield remarkably and would increase the cost of the end product.

The following non-limiting example illustrates the preparation of one of the N-alkylamides (I) according to the process of this invention.

Example

Preparation of D(+)-N-dodecylcarnitinamide chloride

A mixture of dodecylamine (25 m moles), ethylene glycol (20.0 grams) and 85% H_3PO_4 (25 m moles) was reacted in a 100-ml round bottom flask, sealed with a rubber stopper, under stirring, at 130°C for 3 hours under nitrogen.

A mixture of D(+)-carnitinamide chloride (50 m moles) and dodecylamine (55 m moles) was then added to the reaction mixture.

The resulting mixture was kept under stirring at 120°C for 36 hours under nitrogen. When ammonia development ceased, the reaction mixture was cooled and ethylene glycol caused to evaporate at 80°C under 0.5 mm Hg.

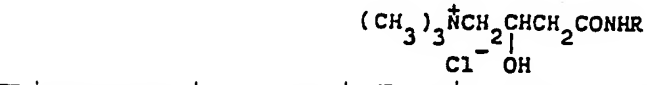
After the residue was dissolved in 80 ml of chloroform, the resulting solution was chromatographed on a silica (50 g) containing column. The product was first eluted with chloroform (100 ml) and with 100 ml of a 9:1 chloroform:isopropanol mixture; then, the product was eluted with 300 ml of a 1:1 chloroform:methanol mixture. The product was recovered by evaporation from the solvent. By further crystallization from 100 ml of tetrahydrofurane and then 100 ml of a 1:1 chloroform:tetrahydrofurane mixture (twice repeated) the title compound was obtained.

(Yield: 70%), $[\alpha]_D^{25}$ + 12.74

Elementary analysis:

C=62.22%; H=11.54%; N=7.56%; Cl=10.2%; O=8.48%

Also the remaining N-alkylamides of D(+)-carnitine chloride encompassed in the general formula (I) were prepared by the same process. In the following table, the main chemico-physical characteristics of the compounds are listed.



R	Abbreviated name	Molecular weight	$[\alpha]_D^{25}$	Elementary Analysis Theoretical (%)	Elementary Analysis Found (%)
$C_{10}H_{21}$	D(+) CA-10	336.92	+13.69°	C= 60.60 H= 10.77 N= 8.31 Cl= 10.52 O= 9.50	C=60.38 H=11.54 N= 8.67 Cl= 10.80 O= 8.61
$C_{11}H_{23}$	D(+) CA-11	350.97	+13.03°	C= 61.60 H= 10.91 N= 7.98 Cl= 10.10 O= 9.12	C= 61.03 H= 11.20 N= 7.75 Cl= 9.80 O= 10.22
$C_{12}H_{25}$	D(+) CA-12	364.97	+12.74°	C= 62.53 H= 11.05 N= 7.68 Cl= 9.71 O= 8.77	C= 62.22 H= 11.54 N= 7.56 Cl=10.2 O= 8.48
$C_{13}H_{27}$	D(+) CA-13	379.03	+12.46°	C= 63.34 H= 11.17 N= 7.39 Cl= 9.35 O= 8.44	C= 63.25 H= 10.51 N= 7.50 Cl= 9.62 O= 9.12
$C_{14}H_{29}$	D(+) CA-14	393.03	+12.00°	C= 64.18 H= 11.28 N= 7.13 Cl= 9.02 O= 6.14	C= 64.04 H= 12.08 N= 7.10 Cl= 9.97 O= 6.81
$C_{15}H_{31}$	D(+) CA-15	407.08	+11.53°	C= 64.91 H= 11.39 N= 6.88 Cl= 8.71 O= 7.86	C= 64.80 H= 11.92 N= 6.80 Cl= 8.50 O= 7.98
$C_{16}H_{33}$	D(+) CA-16	421.08	11.00°	C= 65.61 H= 11.49 N= 6.65 Cl= 8.42 O= 7.60	C= 63.38 H= 11.67 N= 6.62 Cl= 9.47 O= 8.86

IR spectra

Freq. cm^{-1}	Assignments
950	- OH
1300	- CN -
1470	CH_2 e OH
1560	- NH -
1650	C(=O)-NH-
2940	OH
3300	OH

The frequencies and the corresponding assignments can be regarded as identical for all the compounds because the differences between them are not significant.

Toxicological Tests

1. Acute toxicity

(1.1) Acute toxicity via the oral route in mice

It was evaluated in albino Swiss mice weighing 20—25 g which had been kept fasting 12 hours before administration.

The compounds dissolved in distilled water were administered to the animals by gavage.

The animals were divided in groups of 6 animals each and treated with solutions of diminishing concentrations, each concentration being one half of the preceding concentration.

The mice were checked for 7 days following administration in order to verify their possible death or any behavioural alteration.

LD_{50} was evaluated by the Carrol Weil method (Biometrics, Sept. 1952, pages 249—255, "Calculation of median-effective dose").

The results thus obtained are illustrated in Table 1.

Table 1: Acute Toxicity via the oral route in mice

	D(+) CA-10	D(+) CA-12	D(+) CA-14	D(+) CA-16
LD_{50} (mg/kg)	890	1417	1125	1960
Dose (mg/kg)				
4000	–	6/6	6/6	6/6
2000	6/6	6/6	6/6	2/6
1000	4/6	0/6	2/6	0/6
500	0/6	0/6	0/6	0/6
250	0/6	–	–	–

(1.2) Acute toxicity via the intravenous r ute in mice

It was evaluated in albino Swiss mice weighing 20—25 g.

The animals were injected the compounds dissolved in saline solution, in their caudal vein.

The animals were divided in groups of 6 animals each and treated with solutions of diminishing concentration, each concentration being one half of the preceding concentration. The mice were checked for 48 hours following administration.

LD_{50} was evaluated by the Carrol Weil method.

The results are illustrated in table 2.

Table 2: Acute Toxicity via the intravenous route in mice

	D(+) CA-10	D(+) CA-12	D(+) CA-14	D(+) CA-16
LD_{50} (mg/kg)	25.19	25.2	48.72	56.42
Dose (mg/kg)				
160	–	–	6/6	6/6
80	6/6	6/6	6/6	6/6
40	6/6	6/6	3/6	0/6
20	1/6	1/6	0/6	0/6
10	0/6	0/6	–	–

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(1.3) Assessment f the irritating activity on the rabbit eye

The Federal Register test (vol. 38, 1973) modified as hereinbelow indicated was used.

Six New Zealand albino rabbits, weighing 1.5—2 kgs, were used for each test substance. Throughout the test the animals were caged so as to exclude possible extraneous materials that may produce eye irritation.

0.1 ml of a 1% solution of the test compounds was instilled with a dropper into the conjunctival sac of the rabbit right eye (the contralateral eye remained untreated and served as a control), whereupon the animals were caged again.

The treated eyes of all the animals were examined, in comparison the control eye, 24, 48 and, if necessary, 72 hours following treatment.

The irritating activity was rated based on the scoring scale outlined in table 3.

The results are illustrated in table 4.

TABLE 3

Assessment of the irritating activity on the rabbit eye

	Conjunctivae	
a)	Congestion	
	— Vessels normal	0
	— Vessels slightly injected	1
	— Diffuse redness, vessels definitely injected not easily discernible	2
	— Diffuse, beefy red	3
b)	Chemosis	
	— No oedema	0
	— Slight oedema	1
	— Severe oedema with eversion of lids	2
	— Severe oedema with lids about half closed	3
	— Severe oedema with lids more than half closed	4
	Cornea	
	— No alteration or opacity	0
	— Scattered or confluent areas of opacity; details of iris visible	1
	— Easily discernible translucent areas; details of iris slightly obscured	2
	— Nacreous area; no details of iris visible; contours of pupil barely discernible	3
	— Complete corneal opacity; iris not discernible	4
	Iris	
	— Normal	0
	— Markedly deepened folds, more numerous than normal; congestion, swelling, moderate circumcorneal injection; iris still reacting to light	1
	— No reaction to light; haemorrhage; gross destruction	2

Table 4: Assessment of the irritation activity on the rabbit eye

	D(+) CA-10	D(+) CA-12	D(+) CA-14	D(+) CA-16
	irritation score	irritation score	irritation score	irritation score
RABBIT No. 1	0	4	2	6
2	2	4	4	4
3	0	4	2	2
4	2	2	2	2
5	2	2	2	6
6	0	4	2	2
Average score	1	3.3	2.3	3.6

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(1.4) Assessment of the cutaneous irritati n activity in rabbits

Irritation to the skin was evaluated by the meth d illustrated in Federal Register (vol. 38, No. 187, page 27019, 1973) on albino rabbits weighing about 2 kgs.

Tw days bef re the test was commenced, the back of the rabbits was clipped free of hair with an electric shearing machine, taking care not to bring about irritations and abrasions.

At test beginning, a zone of the skin was abraded by a sterile syringe needle.

Both on the intact and abraded skin an AL-test patch soaked in a 20% solution of the test compound was secured in place.

Similar patches (controls) soaked in the same volume of saline solution were secured in place on the intact and abraded skin.

The AL-test patches were secured in place to the animals by antiallergic adhesive plasters.

After 24 hours of exposures the patches were removed and the skin examined.

The reactions were evaluated at 24 and 72 hours on the basis of the table in Federal Register (see table 5). The results thus obtained are illustrated in table 6.

TABLE 5

Assessment of the cutaneous irritating activity

Skin Reactions:		
1) Erythema		
	No erythema	0
	Slight barely perceptible erythema	1
	Well-defined erythema	3
	Moderate to severe erythema	3
	Severe erythema (intense redness) to slight eschar formation	4
2) Oedema		
	No oedema	0
	Slight, barely perceptible oedema	1
	Slight oedema (with well-defined edges)	2
	Moderate oedema (raised approximately 1 mm)	3
	Severe oedema (raised more than 1 mm and extending beyond the exposure area)	4

non-irritating	if the score is 0
mildly irritating	if the score ranges between 0 and 2
averagely irritating	if the score ranges between 2 and 5
severely irritating	if the score ranges between 5 and 8

Table 6: Assessment of the cutaneous irritating activity

Rabbit	Skin	D(+) CA-10 (*)					D(+) CA-12 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
1	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
2	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
3	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
4	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
5	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
6	intact	0	0	0	0	0	0	0	2	0	4
	abraded	0	0	0	0	0	0	0	2	0	
irritation score		0					1				

(*) Exposure period: 4 hours
(**) Exposure period: 24 hours

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Table 6 (cont.): Assessment of the cutaneous irritating activity

Rabbit	Skin	D(+) CA-14 (*)					D(+) CA-16 (**)				
		Erythema value after		Oedema value after		Total	Erythema value after		Oedema value after		Total
		24 hours	72 hours	24 hours	72 hours		24 hours	72 hours	24 hours	72 hours	
	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
2	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
3	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
4	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
5	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
6	intact	0	0	0	0	0	0	0	0	0	0
	abraded	0	0	0	0	0	0	0	0	0	0
irritation score		0					0				

(*) Exposure period: 24 hours
(**) Exposure period: 4 hours

Antibacterial Activity

in vitro

1.1 Determination f antibacterial activity on P tri plates

The test was carried out on sterile Petri plates (14 cm of diameter), by inoculating the strains listed at point A in suitable culture media by the Kirby-Bauer method.

A)

1 — Bacillus subtilis ATCC 6633 on Müller Hinton agar
2 — Escherichia coli ATCC 24922 on Müller Hinton agar
3 — Staphylococcus aureus ATCC 6538 on Müller Hinton agar
4 — Mucor mucedo ATCC 7941 on Sabouraud maltose agar
5 — Candida albicans ATCC 2091 on Sabouraud maltose agar

The antibacterial activity of the compounds was evaluated by means of a well on the solidified medium. The results are shown in table 7.

Table 7: Antibacterial Activity (diameter in mm)

Concentration	Compound	E. coli	Staph. aureus	Bac. subtilis	Cand. albic.	Mucor mucedo (*)
0.1%	C10	10.0	10.2	13.0	12.1	+-
	C12	19.7	16.8	18.6	17.1	+
	C14	11.6	11.3	10.0	13.1	+-
	C16	10.0	10.0	9.5	12.5	+
1%	C10	13.8	15.6	26.8	21.0	++
	C12	28.0	19.7	24.0	23.8	++
	C14	12.0	13.0	12.1	15.8	+
	C16	10.0	12.3	11.5	14.1	+
10%	C12	31.6	20.7	27.8	25.9	+++
	C14	15.5	18.4	17.9	18.3	+
	C16	11.2	15.6	14.0	16.1	+
	DL-carnitinamide-chloride	-	-	-	-	-

(*) +- = 10.0 to 12.0 mm in diameter
+ = 12.0 to 19.0 mm in diameter
++ = 19.0 to 29.0 mm in diameter
+++ = 29.0 to 35.0 mm in diameter

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in vitr

2.1 Determination of Minimum Inhibiting C ncentration (MIC)

The test was carried out n sterile Petri dishes (10 cm of diameter) loaded with 10 ml f medium and antibacterial substance at given c ncentration, mixed at 9:1 ratio.

The medium used was

(1) Müller Hinton agar for bacteria, and

(2) Sabouraud Dextrose agar for fungi

The solidified plates were then inoculated at the surface thereof with a multi-point inoculator equipped with 48 rods, each of which had been coated with a suspension of the tested microorganism. The suspensions were prepared with the Kirby-Bauer method (Bauer, Kirby, Sherris, Turck 1966, Am. J. Clin. Pathol. 45:49—496) modified according to D'Amato-Hochstein (D'Amato-Hochstein, 1982, J. Clin. Microb. 15 (2) 282—285).

The inoculated plates were incubated at 35°C (culture medium (1)) and 25°C (culture medium (2)) respectively.

Reading was carried out after 15—18 hours for bacteria and after 24—30 hours for fungi.

MIC values thus obtained are shown in table 8.

Table 8: Minimum Inhibiting Concentration (mcg)

Method: Petri dishes with solid culture medium

		D(+) CA-10	D(+) CA-12	D(+) CA-14	D(+) CA-16
Staphylococcus aureus	10547	62	15	15	15
"	8530	62	31	15	15
"	6538P	62	62	250	> 500
"	80R	62	15	15	15
"	58R	62	31	15	15
Enterococcus	1 Renz.	62	7	< 7	< 7
"	2 Renz.	62	7	< 7	< 7
Strept. faecalis lactis R	8043	62	< 7	< 7	< 7
" " "	66/48	62	7	< 7	< 7
" faecium	UM	31	15	< 7	< 7
Sarcina lutea	9341	125	62	62	31
Bacillus subtilis	6633	62	15	15	31
Pseudomonas aeruginosa	3E	> 500	250	> 500	> 500
" "	50F	> 500	125	> 500	> 500
" "	12F	> 500	125	> 500	> 500
Salmonella typhi	SK	125	62	250	> 500
Salmonella typhi	6539	62	31	15	31

Table 8 (cont.): Minimum Inhibiting Concentration (mcg)

Method: Petri dishes with solid culture medium

		D(+) CA-10	D(+) CA-12	D(+) CA-14	D(+) CA-16
Enterobacter cloacae	P99 β-Latt.	250	62	125	>500
Shigella sonnei	SK	125	62	200	>500
Escherichia coli	4	125	62	250	>500
" "	828	250	125	>500	>500
" "	92F	250	62	250	>500
" "	66/46	125	125	>500	>500
" "	R57B	500	125	>500	>500
Klebsiella pneumoniae	IB 1 (pat.)	250	62	250	>500
Candida albicans	A 215	250	62	15	62
" "	i6	250	62	15	62
" "	ISS 562	250	62	15	62
Candida tropicalis	ISS 5705	250	< 7	31	7
Mucor Mucedo	7941	250	15	15	62
Aspergillus niger	9642	500	15	15	15

Antidandruff Activity

in vitro

3.1 D(+)CA-12 activity on Pityrosporum ovalis ATCC 12078

The test was carried out on sterile Petri plates having 10 cm of diameter filled with 10 ml of medium inoculated with the tested microorganism.

Sabouraud maltose agar + 1% Tween 80 was used as culture medium.

The Kirby-Bauer method modified according to D'Amato-Hochstein was used.

The plates after inoculation by means of wells on the agar-containing medium were incubated at 35°C for 48 hours.

The diameter of the growth inhibition zone was 20.8 mm for the 1% solution and 11.0 mm for the 0.1% solution.

3.2 Minimum inhibiting concentration of D(+)CA-12 on Pityrosporum ovalis ATCC 12078

The test was carried out following the method outlined at point 2.1, except that the medium was modified by the addition of 1% Tween 80. The resulting MIC was 25 mcg.

The compounds of the invention are suitable for being compounded into pharmaceutical, cosmetic and over-the-counter (OTC) compositions, such as mouthwashes, external disinfectants, deodorants, shaving creams and the like. It was found that, generally, the optimum concentration of N-alkylamides of formula (I) in the compositions is 0.1—0.3% by weight for a preservative action and 0.3—1% by weight for a disinfectant action.

Some compositions according to the invention are hereinbelow indicated.

Alcoholic deodorant

Ethanol	42 g
Perfume	0.1 g
D(+)CA-12	0.1 g
Propylene glycol	3 g
Softigen 767	0.5 g
Deionized water	balance to 100 g

Alcohol-free deodorant

Ethanol	3 g
Solulan C 24	1 g
Perfume	0.1 g
Propylene glycol	3 g
D(+)CA-12	0.1 g
Lanidrol (lanolin alcohol)	0.5 g
Deionized water	balance to 100 g

Shaving cream

Esso wax 5250	6 g
Marcol 52	6.5 g
Laurex CS	10 g
Tween 60	3 g
Silicone oil AK 350	1 g
Butylhydroxyanisole	0.05 g
Steinamid P256	1.7 g
D(+)CA-12	0.15 g
EDTA (ethylenediaminetetraacetic acid)	0.2 g
Propylene glycol	3 g
Empigen BT	5 g
Polimer JR 400	0.1 g
Perfume	0.35 g
Deionized water	balance to 100 g

Liquid detergent

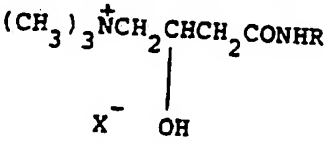
Empilan 2574	1 g
Tween 20	2.4 g
Tween 80	1.5 g
Empigen BT	40 g
Zetesol 250	7.6 g
Neo extrapon lemon	0.1 g
Sigma antioxidant	0.1 g
EDTA	0.1 g
D(+)CA-12	0.15 g
Solulan 16	0.6 g
Phosphoric acid	0.12 g
Coconut oil diethanolamide	3 g
Deionized water	balance to 100 g

Chewing gum

Chlorofil	0.0027 g
Sodium fluoride	0.0152 g
D(+)CA-12	0.667 g
Micronized sorbitol	35.78 g
Micronized mannitol	13.55 g
Gum base	28.74 g
Aroma	0.282 g
Menthol	0.406 g
70% sorbitol solution	17.35 g

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. N-alkylamides of D(+)-carnitine having general formula (I)

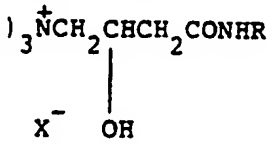


(I)

wherein:
X^- is OH^- or the anion of a pharmacologically acceptable acid, and
R is a straight C_{10}—C_{16} alkyl radical.

2. N-alkylamides of D(+)-carnitine according to claim 1, wherein X^- is Cl^-.

3. A process for preparing N-alkylamides f D(+)-carnitine having g neral formula (I)



(I)

wherein:

X^- is OH^- or the anion of a pharmacologically acceptable acid, and

R is a straight C_{10}—C_{16} alkyl radical which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}—C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120—140°C, for 2—4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture, a mixture of D(+)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of D(+)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110—130°C for about 34—48 hours in an atmosphere of inert gas.

4. The process of claim 3, wherein the high-boiling solvent is ethylene glycol.

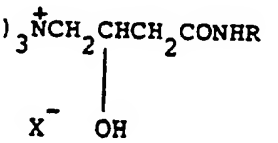
5. A composition suitable for topical application having antibacterial activity which comprises an amount effective for exerting a disinfectant action of at least one of the N-alkylamides of D(+)-carnitine of claim 1.

6. The composition of claim 5 comprising about 0.3—1.0% by weight of one of the N-alkylamides of D(+)-carnitine of claim 1.

7. The composition of claim 5 or 6 in the form of a mouthwash, external disinfectant, deodorant, face cream, body cream and shaving cream.

Claims for the Contracting States: AT ES

1. A process for preparing N-alkylamides of D(+)-carnitine having general formula (I)



(I)

wherein:

X^- is OH^- or the anion of a physiologically acceptable acid, and

R is a straight C_{10}—C_{16} alkyl radical which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}—C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120—140°C, for 2—4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture, a mixture of D(+)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of D(+)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110—130°C for about 34—48 hours in an atmosphere of inert gas.

2. The process of claim 1, wherein the high-boiling solvent is ethylene glycol.

3. Application of the N-alkylamides of D(+)-carnitine obtained with the process according to claim 1 or 2 to the preparation of cosmetic compositions.

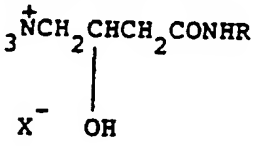
4. A cosmetic composition suitable for topical application which comprises at least one of the N-alkylamides of D(+)-carnitine obtained with the process according to claim 1 or 2.

5. The composition of claim 4 comprising about 0.3—1.0% by weight of one of the N-alkylamides of D(+)-carnitine obtained with the process according to claim 1 or 2.

6. The composition of claim 4 or 5 in the form of a deodorant, face cream, body cream and shaving cream.

Claims for the Contracting State: GR

1. N-alkylamides of D(+)-carnitine having general formula (I)



(I)

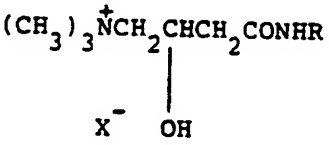
wherein:

X^- is OH^- or the anion of a physi logically acceptable acid, and

R is a straight C_{10}—C_{16} alkyl radical.

2. N-alkylamides of D(+)-carnitine according to claim 1, wherein X^- is Cl^-.

3. A process for preparing N-alkylamides of D(+)-carnitine having general formula (I)



(I)

wherein:

X^- is OH^- or the anion of a physiologically acceptable acid, and

R is a straight C_{10}—C_{16} alkyl radical which comprises the steps of

(a) reacting an alkylamine of formula NH_2R wherein R is a straight C_{10}—C_{16} alkyl radical with a substantially equimolar amount of H_3PO_4, at 120—140°C, for 2—4 hours, in an atmosphere of an inert gas, in the presence of a high-boiling solvent; and

(b) adding to the reaction mixture, a mixture of D(+)-carnitinamide chloride and alkylamine NH_2R, at a molar ratio of about 1:1.1, the molar amount of D(+)-carnitinamide chloride being about twice as much the molar amount of H_3PO_4 and keeping the resulting reaction mixture under stirring at about 110—130°C for about 34—48 hours in an atmosphere of inert gas.

4. The process of claim 3, wherein the high-boiling solvent is ethylene glycol.

5. Application of the N-alkylamides of D(+)-carnitine of claim 1 to the preparation of cosmetic compositions.

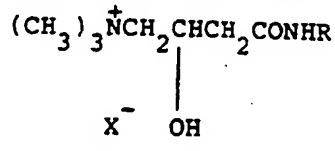
6. A cosmetic composition suitable for topical application which comprises at least one of the N-alkylamides of D(+)-carnitine of claim 1.

7. The composition of claim 6 comprising about 0.3—1.0% by weight of one of the N-alkylamides of D(+)-carnitine of claim 1.

8. The composition of claim 6 or 7 in the form of a deodorant, face cream, body cream and shaving cream.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. N-Alkylamide von D(+)-Carnitin der allgemeinen Formel (I)



(I)

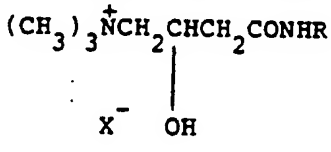
worin bedeuten:

X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und

R einen geradkettigen C_{10}—C_{16} Alkylrest

2. N-Alkylamide von D(+)-Carnitin gemäß Anspruch 1, worin X^- Cl^- ist.

3. Verfahren zur Herstellung von N-Alkylamiden von D(+)-Carnitin der allgemeinen Formel (I)



(I)

worin bedeuten:

X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und

R einen geradkettigen C_{10}—C_{16} Alkylrest

welches die Stufen umfaßt:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10}—C_{16} Alkylrest ist mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140°C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionsgemisch einer Mischung von D(+)-Carnitinamid-Chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1.1, wobei das Molverhältnis v n D(+)-Carnitinamid-Chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110—130°C während etwa 34 bis 38 Stunden in einer Inertgasatmosphäre rührt.

4. Verfahren gemäß Anspruch 3, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

5. Zusammensetzung für eine topische Anwendung mit antibaktiereller Aktivität, umfassend eine

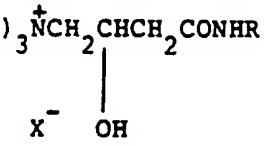
Menge, die wirksam eine Desinfizierwirkung ausübt, an wenigstens einem der N-Alkylamide des D(+)-Carnitins gemäß Anspruch 1.

6. Zusammensetzung gemäß Anspruch 5, umfassend etwa 0,3 bis 1,0 Gew.-% eines der N-Alkylamide des D(+)-Carnitins von Anspruch 1.

7. Zusammensetzung gemäß Ansprüchen 5 oder 6 in Form einer Mundspülung, eines äußeren Desinfektionsmittels, eines Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Patentansprüche für die Vertragsstaaten: AT ES

1. Verfahren zur Herstellung von N-Alkylamiden von D(+)-Carnitin der allgemeinen Formel (I)



(I)

worin bedeuten:

X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und

R einen geradkettigen C_{10}—C_{16} Alkylrest

welches die Stufen umfaßt:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10}—C_{16} Alkylrest ist mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140°C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionsgemisch einer Mischung von D(+)-Carbinitinamid-Chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1.1, wobei das Molverhältnis von D(+)-Carnitinamid-Chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110—130°C während etwa 34 bis 38 Stunden in einer Inertgasatmosphäre rührt.

2. Verfahren gemäß Anspruch 1, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

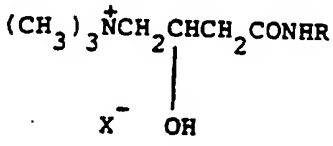
3. Anwendung von N-Alkylamiden von D(+)-Carnitin erhalten nach dem Verfahren gemäß Ansprüchen 1 oder 2 für die Herstellung von kosmetischen Zusammensetzungen.

4. Kosmetische Zusammensetzung, die für die topische Anwendung geeignet ist, umfassend wenigstens eines der N-Alkylamide des D(+)-Carnitins, erhalten nach dem Verfahren gemäß Anspruch 1 oder 2.

5. Zusammensetzung gemäß Anspruch 4, umfassend etwa 0,3 bis 1,0 Gew.-% eines der N-Alkylamide von D(+)-Carnitin, erhalten nach dem Verfahren gemäß Anspruch 1 oder 2.

6. Zusammensetzung gemäß Anspruch 4 oder 5 in Form eines Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Patentansprüche für den Vertragsstaat: GR



(I)

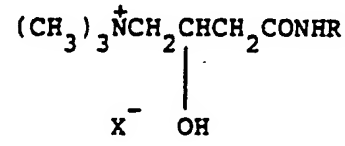
worin bedeuten:

X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und

R einen geradkettigen C_{10}—C_{16} Alkylrest

2. N-Alkylamide von D(+)-Carnitin gemäß Anspruch 1, worin X^- Cl^- ist.

3. Verfahren zur Herstellung von N-Alkylamiden von D(+)-Carnitin der allgemeinen Formel (I)



(I)

worin bedeuten:

X^- OH^- oder das Anion eines pharmakologisch annehmbaren Salzes, und

R einen geradkettigen C_{10}—C_{16} Alkylrest

welches die Stufen umfaßt:

(a) Umsetzen eines Alkylamins der Formel NH_2R, worin R ein geradkettiger C_{10}—C_{16} Alkylrest ist mit einer im wesentlichen äquimolaren Menge von H_3PO_4 bei 120 bis 140°C während 2 bis 4 Stunden in einer Inertgasatmosphäre in Gegenwart eines hochsiedenden Lösungsmittels; und

(b) Zugabe zu dem Reaktionsgemisch einer Mischung von D(+)-Carbinitinamid-Chlorid und Alkylamin NH_2R in einem Molverhältnis von etwa 1:1.1, wobei das Molverhältnis von D(+)-Carnitinamid-Chlorid etwa zweimal der molaren Menge von H_3PO_4 entspricht, und wobei man die erhaltene Reaktionsmischung bei etwa 110—130°C während etwa 34 bis 38 Stunden in einer Inertgasatm sphäre rührt.

4. Verfahren gemäß Anspruch 3, bei dem das hochsiedende Lösungsmittel Ethylenglykol ist.

5. Anwendung von N-Alkylamiden von D(+)-Carnitin gemäß Anspruch 1 zur Herstellung von kosmetischen Zusammensetzungen.

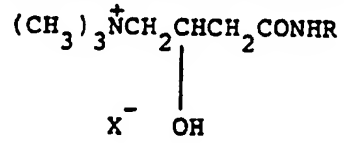
6. Kosmetische Zusammensetzung, die für eine topische Anwendung geeignet ist, welche wenigstens eines der N-Alkylamide des D(+)-Carnitins von Anspruch 1 umfaßt.

7. Zusammensetzung gemäß Anspruch 6, umfassend etwa 0,3 bis 1,0 Gew.-% eines der N-Alkylamide von D(+)-Carnitin gemäß Anspruch 1.

8. Zusammensetzung gemäß Anspruch 6 oder 7 in Form eines Deodorants, einer Gesichtscreme, einer Körpercreme und einer Rasiercreme.

Revendications pour les Etats contractants: BE CH DE FR GB LI LU NL SE

1. N-alkylamides de O(+)-carnitine, ayant la formule générale (I):



(I)

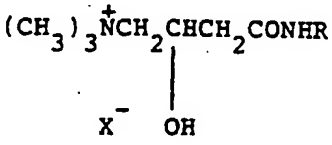
dans laquelle:

X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et

R est un radical alkyle en C_{10-16} à chaîne droite.

2. N-alkylamides de O(+)-carnitine suivant la revendication 1, caractérisés en ce que X^- est Cl^-.

3. Procédé de préparation de N-alkylamides de O(+)-carnitine, ayant la formule générale (I):



(I)

dans laquelle:

X^- est OH^- ou l'anion d'un acide acceptable du point de vue pharmaceutique et

R est un radicaly alkyle en C_{10-16} à chaîne droite, caractérisé en ce qu'il comprend les étapes suivantes:

(a) réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120—140°C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et

(b) addition au mélange réactionnel d'un mélange de chlorure de O(+)-carnitidinamide et d'alkylamine NH_2R, en un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de O(+)-carnitinamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110—130°C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

4. Procédé suivant la revendication 3, caractérisé en ce que le solvant à haut point d'ébullition est l'éthylène glycol.

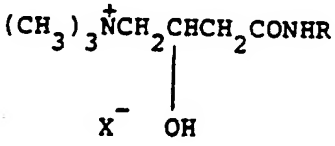
5. Composition convenable pour l'application topique ayant une activité antibactérienne, caractérisée en ce qu'elle comprend une quantité efficace pour exercer une action désinfectante d'au moins l'un des N-alkylamides de O(+)-carnitine suivant la revendication 1.

6. Composition suivant la revendication 5, caractérisée en ce qu'elle comprend d'environ 0,3 à 1,0% en poids d'un des N-alkylamides de O(+)-carnitine suivant la revendication 1.

7. Composition suivant la revendication 5 ou la revendication 6, caractérisée en ce qu'elle est sous forme d'eau d'entifrice, de désinfectant externe, de déodorant, de crême pour le visage, de crème pour le corps et de crème à raser.

Revendications pour les Etats contractants: AT ES

1. Procédé de préparation de N-alkylamides de D[+]-carnitine, ayant la formule générale [I]:



(I)

dans laquelle:

X^- est OH^- u l'anion d'un acide acceptable du point de vue physiologique et R est un radical alkyle en C_{10-16} à chaîne droite, caractérisé en ce qu'il comprend les étapes suivantes:

[a] réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120°C—140°C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et

[b] addition au mélange réactionnel d'un mélange de chlorure de D[+]-carnitinamide et d'alkylamine NH_2R, en un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de D[+]-carnitinamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110—130°C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

2. Procédé suivant la revendication 1, caractérisé en ce que le solvant à haut point d'ébullition est l'éthylène glycol.

3. Application des N-alkylamides de D[+]-carnitine obtenus selon le procédé de la revendication 1 ou 2, à la préparation de compositions cosmétiques.

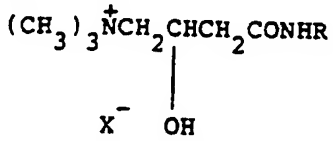
4. Composition cosmétique convenable pour l'application topique comprenant au moins l'un des N-alkylamides de D[+]-carnitine obtenus selon le procédé suivant la revendication 1 ou 2.

5. Composition suivant la revendication 4 comprenant d'environ 0,3 à 1,0% en poids d'un des N-alkylamides de D[+]-carnitine obtenus selon le procédé suivant la revendication 1 ou 2.

6. Composition suivant la revendication 4 ou la revendication 5 sous forme de déodorant, de crème pour le visage, de crème pour le corps et de crème à raser.

Revendications pour l'Etat contractant: GR

1. N-alkylamides de D(+)-carnitine, ayant la formule générale (I):



(I)

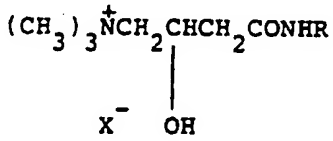
dans laquelle:

X^- est OH^- ou l'anion d'un acide acceptable du point de vue physiologique et

R est un radical alkyle en C_{10-16} à chaine droite.

2. N-alkylamides de D(+)-carnitine suivant la revendication 1, caractérisés en ce que X^- est Cl^-.

3. Procédé de préparation de N-alkylamides de D(+)-carnitine, ayant la formule générale (I):



(I)

dans laquelle:

X^- est OH^- ou l'anion d'un acide acceptable du point de vue physiologique et

R est un radical alkyle en C_{10-16} à chaine droite, caractérisé en ce qu'il comprend les étapes suivantes:

(a) réaction d'une alkylamine de formule NH_2R dans laquelle R est un radical alkyle en C_{10-16} à chaîne droite avec une quantité pratiquement équimolaire de H_3PO_4, à 120—140°C pendant 2 à 4 heures, dans une atmosphère de gaz inerte, en présence d'un solvant à point d'ébullition élevé; et

(b) addition au mélange réactionnel d'un mélange de chlorure de D[+]-carnitinamide et d'alkylamine NH_2R, en un rapport molaire d'environ 1/1,1, la quantité molaire du chlorure de D[+]-cartininamide étant environ deux fois la quantité molaire de H_3PO_4 et agitation du mélange réactionnel résultant à environ 110—130°C pendant environ 34 à 38 heures sous atmosphère de gaz inerte.

4. Procédé suivant la revendication 3, caractérisé en ce que le solvant à haut point d'ébullition est l'éthylène glycol.

5. Application des N-alkylamides de D(+)-carnitine de la revendication 1 à la préparation de compositions cosmétiques.

6. Composition cosmétique pour l'application topique comprenant au moins l'un des N-alkylamides de D(+)-carnitine suivant la revendication 1.

7. Composition suivant la revendication 6 comprenant environ 0,3 à 1,0% en poids d'un des N-alkylamides de D(+)-carnitine suivant la revendication 1.

8. Composition suivant la revendication 6 ou la revendication 7 sous forme de déodorant, de crème pour le visage, de crème pour le corps et de crème à raser.